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(54) 5,6-Dihydro-2-(substituted phenyl)-1,2,4-triazine-3,5(2H,4H)-diones.

The file contains technical information submitted after the application was filed and not included in this specification

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EP-A- 0 154 885
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FR-A- 2 231 378
US-A- 3 912 723

(73) Proprietor: JANSSEN PHARMACEUTICA N.V.
Turnhoutseweg 30
B-2340 Beerse (BE)

(72) Inventor: Boeckx, Gustaaf Maria
Augustijnenstraat 21
B-2360-Oud-Turnhout (BE)
Inventor: Raeymaekers, Alfons Herman Margaretha
Aanbeeldstraat 1
B-2340-Beerse (BE)
Inventor: Sipido, Victor
Winterkoningstraat 37
B-2060-Merksem (BE)

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Description

2-Phenyl-as-triazine-3,5(2H,4H)-diones and their use for controlling coccidiosis have been described in U.S. Patent No. 3,912,729. The phenyl moiety in the said triazines may, inter alia, be substituted with a benzoyl-, an α-hydroxy-phenylmethyl- and a phenylsulfonyl radical.

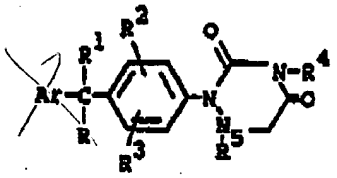
Substituted 2-phenyl-hexahydro-1,2,4-triazine-3,5-diones and their use for combatting Protozoa have been disclosed in Published Eur. Pat. Application No. 0,154,885.

The 5,6-dihydro-2-phenyl-1,2,4-triazine-3,5(2H,4H)-diones, described in the present application, differ from the hereinabove-mentioned triazinones, by the specific substitution of the 2-phenyl moiety, resulting in 5,6-dihydro-1,2,4-triazine-3,5(2H,4H)-diones which are very effective in destructing or preventing the growth of Protozoa in subjects suffering from such Protozoa.

A number of compounds structurally closely related to the ones the present invention are disclosed in EP-A-0 170 316, some of such compounds being excluded by provisions from the definition of the compounds of formula (II-J) as defined hereafter.

Description of the preferred embodiments :

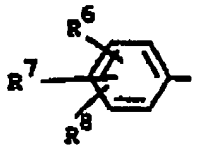
The present invention is related to 5,6-dihydro-2-(substitutedphenyl)-1,2,4-triazine-3,5(2H,4H)-diones having the formula



(I),

the pharmaceutically acceptable acid addition, metal or amine substitution salts, and stereochemically isomeric forms thereof, wherein :

Ar is thienyl, halo substituted thienyl, naphthalenyl or a radical of formula



(a);

R is hydrogen, C_{1-6} alkyl, cyclo C_{3-6} alkyl, aryl or (aryl)C_{1-6} alkyl ;
R^1 is cyano or a radical of formula -C(=X)-Y-R^9 ;
said X being O or S,
Y being O, S, NR^{10} or a direct bond ; R^9 being hydrogen, aryl, C_{3-6} cycloalkyl or C_{1-6} alkyl optionally substituted with aryl, hydroxy, amino, mono- and di(C_{1-6} alkyl)amino, piperidinyl, pyrrolidinyl, 4-morpholinyl, piperazinyl, 4-(C_{1-6} alkyl)-piperazinyl, 4-(C_{1-6} alkyl-carbonyl)-piperazinyl, 4-(C_{1-6} alkyloxycarbonyl)-piperazinyl or 4-((aryl) C_{1-6} alkyl)-piperazinyl ; and where Y is a direct bond, R^9 may also be halo ; R^{10} is hydrogen, C_{1-6}alkyl or (aryl) C_{1-6}alkyl ; or R^9 and R^{10} taken together with the nitrogen atom bearing said R^9 and R^{10} may form a piperidinyl, pyrrolidinyl, 4-morpholinyl, piperazinyl, 4-(C_{1-6} alkyl)piperazinyl, 4-(C_{1-6}alkylcarbonyl)-piperazinyl, 4-(C_{1-6}alkyloxycarbonyl)-piperazinyl or a 4-((aryl) C_{1-6} alkyl)-piperazinyl radical ;
R^2, R^3, R^6, R^7 and R^8 are each independently hydrogen, halo, trifluoromethyl, C_{1-6} alkyl, hydroxy, C_{1-6} alkyloxy, C_{1-6} alkylcarbonyloxy, mercapto, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, (trifluoromethyl)-sulfonyl, cyano, nitro, amino, mono- and di(C_{1-6} alkyl)amino, or (C_{1-6} alkylcarbonyl)amino ;
R^4 and R^5 are each independently hydrogen, aryl, cyclo C_{3-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, (aryl)C_{2-6} alkenyl or C_{1-6} alkyl optionally substituted with aryl, hydroxy, amino, mono- and di(C_{1-6})amino, piperidinyl, pyrrolidinyl, 4-morpholinyl, piperazinyl, 4-(C_{1-6} alkyl)-piperazinyl, 4-(C_{1-6} alkylcarbonyl)-piperazinyl, 4-(C_{1-6} alkyloxy-carbonyl)-piperazinyl or 4-((aryl) C_{1-6} alkyl)-piperazinyl ;
and R^5 may also be C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl, (aryl)C_{1-6}alkyloxycarbonyl or (aryl)carbonyl ;
wherein aryl is phenyl, optionally substituted with up two 3 substituents each independently selected from

the group consisting of halo, C_{1-6} alkyl, C_{1-6} alkyloxy, trifluoromethyl, hydroxy, mercapto, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, C_{1-6}alkylsulfinyl, trifluoromethylsulfonyl, cyano, nitro, amino, mono-and di (C_{1-6}alkyl)amino and (C_{1-6} alkylcarbonyl)amino.

In the foregoing definitions the term "halo" is generic to fluoro, chloro, bromo and iodo ; "C_{1-6} alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, butyl, pentyl and hexyl "cyclo C_{3-6} alkyl" embraces cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl ; "C_{2-6} alkenyl" is meant to include straight and branch chained hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 3-propenyl and 2-butenyl "C_{2-6} alkynyl" is meant to include straight and branch chained hydrocarbon radicals containing one triple bond and having from 2 to 6 carbon atoms such as, for example, ethynyl, 3-propynyl and 2-butynyl

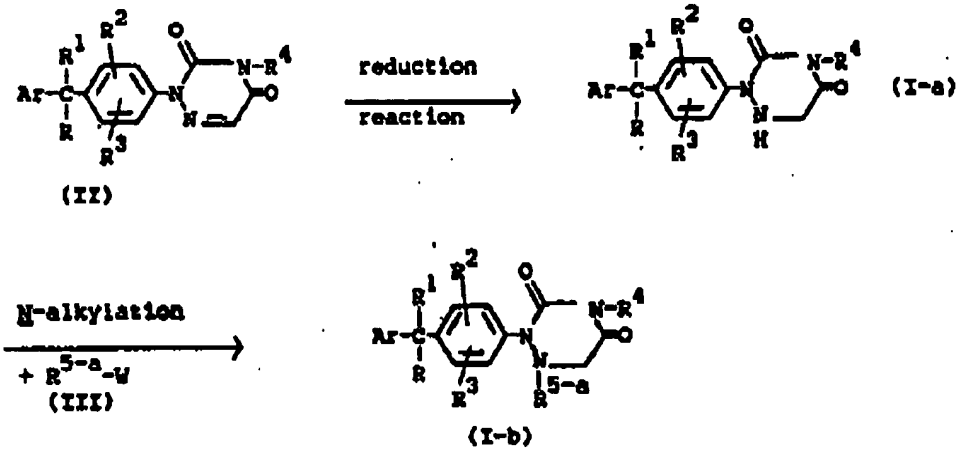
Preferred compounds within the invention are those wherein Ar is halothienyl or a radical of formula (a) wherein R^6 and R^7 are, each independently, hydrogen, halo, trifluoromethyl, C_{1-6} alkyloxy, hydroxy or C_{1-6} alkyl ; R^8 is hydrogen ; R is hydrogen, C_{1-6} alkyl, phenyl or halophenyl ; R^2 and R^3 are, each independently, hydrogen, halo, trifluoromethyl or C_{1-6} alkyl ; and R^4 is hydrogen or C_{1-6} alkyl.

Particularly preferred compounds within the invention are those preferred compounds wherein Ar is a radical of formula (a) wherein R^6 is halo, R^7 and R^8 are hydrogen, R is hydrogen or C_{1-6} alkyl, R^2 and R^3 independently are halo or hydrogen.

More particularly preferred compounds within the invention are those particularly preferred compounds wherein R^6 is 4-chloro, R is hydrogen, R^2 is 2-chloro, R^3 is 6-chloro or hydrogen and R^4 is hydrogen.

The most preferred compounds within the invention are 2,6-dichloro-α-(4-chlorophenyl)-4-(3,4,5,6-tetrahydro-3,5-dioxo-1,2,4-triazin-2(1H)-yl)benzeneacetonitrile and 2-chloro-α-(4-chlorophenyl)-4-(3,4,5,6-tetrahydro-3,5-dioxo-1,2,4-triazin-2(1H)-yl) benzeneacetonitrile and the pharmaceutically acceptable acid addition, metal or amine substitution salts thereof.

The compounds of formula (I) may conveniently be prepared by a reduction reaction of the corresponding 1,2,4-triazine-3,5-(2H,4H)-dione of formula (II), or an acid-addition salt, metal or amine substitution salt form thereof, thus preparing a compound of formula (I) wherein R^5 is hydrogen, said compounds being represented by the formula (I-a), and if desired, subsequently reacting the compounds of formula (I-a) with a reagent R^{5-a}-W (III), thus preparing compounds of formula (I), wherein R^5 is other than hydrogen, said compounds being represented by the formula (I-b). In (III) W represents an appropriate reactive leaving group such as, for example, halo, e.g., chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methylphenyl-sulfonyloxy and R^{5-a} has the previously defined meaning of R^5, provided that it is not hydrogen.

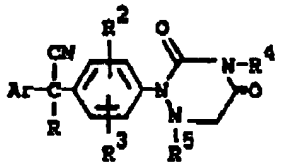


The said reduction reaction is conveniently conducted following art-known procedures for converting a 1,2,4-triazine-3,5-(2H,4H)-dione into a 5,6-dihydro-1,2,4-triazine-3,5(2H,4H)-dione moiety. A number of such procedures are described in for example the Published Eur. Pat. Application No. 0,154,885 and the references cited therein.

Said reduction reaction may for example be conducted by contacting the starting material of formula (II) with hydrogen in the presence of an appropriate catalyst such as, for example, Raney-nickel, platinum, palladium, platinum(IV) oxide, and the like. Preferably, said reduction reaction is conducted by reacting the starting material (II) with zinc in acetic acid or tin(II) chloride in hydrochloric acid, optionally in the presence of a reaction-inert organic solvent or mixture of such solvents such as, for example, a lower alkanol, e.g. methanol or ethanol ; a hydrocarbon, e.g. methylbenzene or dimethylbenzene ; a ketone, e.g. 2-propanone, 1-butanone ; an ether, e.g. tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, an ester, e.g. ethyl acetate; N,N-dimethylformamide, N,N-dimethylacetamide ; pyridine ; acetic acid. Higher temperatures may be used to enhance the reaction rate.

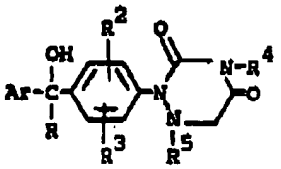
The alkylation reaction of (I-a) with the reagent $R^{5-a}-W$ may be conducted following art-known N-alkylation procedures. The alkylation reaction is conveniently conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene and dimethylbenzene, a lower alkanol, e.g., methanol, ethanol and 1-butanol a ketone, e.g., 2-propanone and 4-methyl-2-pentanone an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane and tetrahydrofuran N,N-dimethylformamide (DMF) ; N,N-dimethylacetamide (DMA) ; nitrobenzene ; dimethyl sulfoxide (DMSO) and 1-methyl-2-pyrrolidinone. The addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, sodium hydride or an organic base such as, for example N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be utilized to pick up the acid which is liberated during the course of the reaction. In some circumstances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures may enhance the rate of the reaction.

The compounds of formula (I) wherein R^1 is cyano, said compounds being represented by the formula



(I-c)

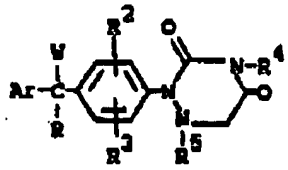
may alternatively be prepared by converting the hydroxy function of a triazinedione of formula



(IV)

into a nitrile function.

The conversion of (IV) into (I-c) may be effected by art-known procedures. For example, by first converting the hydroxy function into a suitable leaving group and subsequently converting the said leaving group in the thus obtained intermediate having the formula



(V)

into a nitrile function.

In (V) W has the meaning of an appropriate reactive leaving group such as, for example, halo, e.g., chloro, bromo or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy or 4-methylphenylsulfonyloxy.